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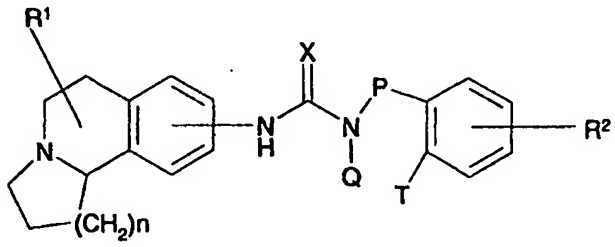

(I)

(57) Abstract

Compound of formula (I) or salts thereof or solvates thereof, in which, P is a single bond, methylene or ethylene; Q is hydrogen or C1–6alkyl; T is hydrogen; or Q and T together are $-(CH_2)_m-$ wherein the saturated ring formed thereby may be substituted by a group R^3; m is 1 or 2; n is 1 or 2; X is O or S; R^1, which may be at any position within the bicyclic saturated ring system, is hydrogen or up to two substituents which may be the same or different and each of which is selected from fluoro and C_{1-6}alkyl; R^2 is hydrogen or up to four substituents independently selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, oxazolyl, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl–C_{1-4}alkyl–, C_{1-6}alkylO–, C_{1-6}alkylCO–, C_{3-6}cycloalkylO–, C_{3-6}cycloalkylCO–, C_{3-6}cycloalkyl–C_{1-4}alkylO–, C_{3-6}cycloalkyl–C_{1-4}alkylCO–, phenyl, phenoxy, benzyloxy, benzoyl, phenyl–C_{1-4}alkyl–, C_{1-6}alkylS–, C_{1-6}alkylSO$_2$–, $(C_{1-4}alkyl)_2NSO_2-$, $(C_{1-4}alkyl)NHSO_2-$, $(C_{1-4}alkyl)_2NCO-$, $(C_{1-4}alkyl)NHCO-$ or $CONH_2$; or $-NR^4R^5$ where R^4 is hydrogen or C_{1-4} alkyl, and R^5 is hydrogen, C_{1-4}alkyl, formyl, $-CO_2C_{1-4}$alkyl or $-COC_{1-4}$alkyl; R^3 is hydrogen or up to two C_{1-6} alkyl groups are indicated to be useful in the treatment and prophylaxis of epilepsy, migraine, and other disorders.

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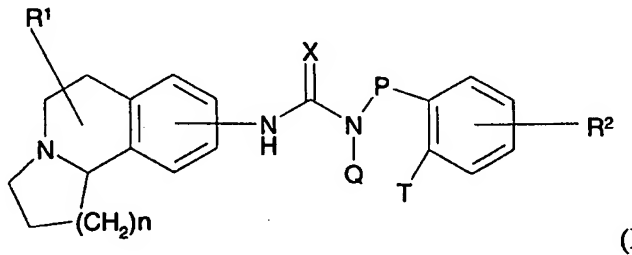
UREA DERIVATIVES

This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

It has now been surprisingly found that tricyclic compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Accordingly, the present invention provides a compound of formula (I) or salt thereof or solvate thereof:



(I)

in which

P is a single bond, methylene or ethylene;

Q is hydrogen or C1-6alkyl;

T is hydrogen;

or Q and T together are $-(CH_2)_m-$ wherein the saturated ring formed thereby may be substituted by a group R^3;

m is 1 or 3;

n is 1 or 2;

X is O or S;

R^1, which may be at any position within the bicyclic saturated ring system, is hydrogen or up to two substituents which may be the same or different and each of which is selected from fluoro and C_{1-6} alkyl;

R^2 is hydrogen or up to four substituents independently selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, oxazolyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO$_2$-, (C_{1-4}alkyl)$_2$NSO$_2$-, (C_{1-4}alkyl)NHSO$_2$-, (C_{1-4}alkyl)$_2$NCO- , (C_{1-4}alkyl)NHCO- or $CONH_2$;
or -NR^4R^5 where R^4 is hydrogen or C_{1-4} alkyl, and R^5 is hydrogen, C_{1-4}alkyl, formyl, -CO_2C_{1-4}alkyl or -COC_{1-4}alkyl;

R^3 is hydrogen or up to two C_{1-6} alkyl groups.

When Q and T together are -$(CH_2)_m$-, the ring structure PNQ formed thereby is unsubstituted or substituted by one or two C_{1-6}alkyl groups, including gem-dialkyl substitution, so that such compounds are tetrahydroisoquinoline, tetrahydroquinoline or dihydroindole ureas.

When Q is hydrogen or C_{1-6}alkyl and T is hydrogen, such compounds are acyclic ureas.

The benzene ring fused to ring structure PNQ may be substituted by up to four, preferably 0, 1, 2 , non-hydrogen R^2 groups.

In the formula (I), alkyl groups, including alkyl groups that are part of another moiety, may be straight chain or branched. Aromatic rings, especially phenyl groups, including rings that are part of another moiety, may optionally be substituted with one or more independently selected halogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl groups. Suitable halo substituents include fluoro, chloro, iodo and bromo. Suitable C_{3-6} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-N-(C_{1-6})alkyl-amino, acylamino, carboxy,

carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryloxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

It should be appreciated that the compounds of formula (I) have one or more chiral carbon atoms and therefore may exist as enantiomers . The present invention extends to each enantiomer and to mixtures thereof including racemates and diastereomers.

A suitable group of compounds of formula (I) have

R^1 as hydrogen, fluoro, methyl, ethyl or propyl,

R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl, *t*-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl,

R^3 as hydrogen or methyl or gem-dimethyl.

In a particular group of compounds of formula (I),

R^1 is hydrogen,

R^2 is hydrogen or one or more of ethyl, methoxy, trifluoromethyl, cyano, chloro, fluoro,

R^3 is hydrogen or gem-dimethyl.

Compounds of formula (I) include:

3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide;

1-(3-Nitrophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;

1-(3-Methoxyphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;

1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;

1-(3-Methylthiophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;

1-(3-Fluorophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;

1-(3-Trifluoromethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)thiourea;

3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide;

1-(3-Bromophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea, and;

1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea.

When synthesised, these compounds may be in salt form, such as the hydrochloride or trifluoroacetate, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and their salts may be obtained as solvates, such as hydrates, and these also form part of this invention.

The above-listed compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, form a preferred aspect of the present invention.

The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, nasal, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Accordingly, in a further aspect, the present invention provides a pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis,

migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

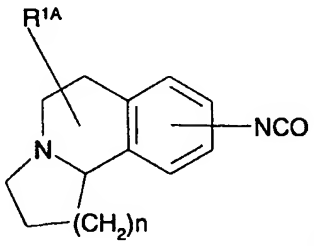
The present invention also provides a method of treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders

(OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

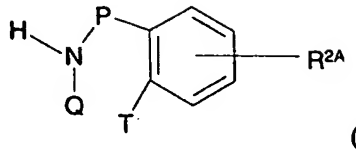
Another aspect of the invention provides a process for the preparation of compounds of formula (I) or salt thereof or solvate thereof, which comprises reacting a compound of formula (II)



(II)

where n is as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1,

with a compound of formula (III)



(III)

where P, Q, and T are as defined for formula (I), and when Q and T together are $-(CH_2)_m-$, the saturated ring formed thereby may be unsubstituted or substituted by a group R^{3A};
R^{2A} and R^{3A} are R^2 and R^3 respectively as defined for formula (I) or a group or groups convertible to R^2 or R^3;
and where required converting a R^{1A} , R^{2A} or R^{3A} group to a R^1, R^2 or R^3 group;
converting one R^1 , R^2 or R^3 group to another R^1 , R^2 or R^3 group;
converting a salt product to the free base or another salt which is pharmaceutically acceptable, or converting a free base product to a pharmaceutically acceptable salt.

When Q and T together are $-(CH_2)_m-$, the compounds of formula (III) are tetrahydroisoquinolines, tetrahydroquinolines or dihydroindoles.

When Q is hydrogen or C_{1-6}alkyl and T is hydrogen, the compounds of formula (III) are exocyclic amines.

Conversions of a R^{1A} , R^{2A} or R^{3A} group to a R^1 , R^2 or R^3 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R^1 , R^2 or R^3 group to another typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

Conventional conditions for condensation of isocyanates with amines may be used, for example treatment in an inert solvent such as toluene, DMF or dichloromethane at ambient or elevated temperature.

The compounds of formula (II) have chiral carbon atoms and therefore may exist as enantiomers. Accordingly the above process may produce compounds of formula (I) that are racemic mixtures. These mixtures may be separated or resolved by conventional procedures if individual enantiomers are required. Alternatively the starting materials may be selected to achieve a stereospecific reaction.

Compounds of formula (II) may be prepared from the corresponding amines using conventional procedures such as described by I T Forbes *et al* , J.Med.Chem., 1993, 36, 1104, and in Fieser and Fieser, Reagents for Organic

Synthesis Vol I. For example an isocyanate may be prepared by stirring a relevant amine with one equivalent of carboxyl diimidazole in a suitable solvent such as dichloromethane at room temperature, and then evaporated to dryness *in vacuo*.

The amine precursor of compounds of formula (II) may be prepared from the corresponding hexahydro-pyrido/pyrollo-isoquinolines, firstly forming a nitro compound and then hydrogenating the nitro group to the amine. The nitro group may be introduced by treating the hexahydro-pyrido/pyrollo-isoquinoline with concentrated sulfuric acid and adding potassium nitrate. Hydrogenation of the nitro compound is suitably carried out by reaction with hydrogen at 50 psi in the presence of palladium/charcoal in a suitable solvent such as ethanol.

The isocyanate of formula (II) may be prepared from the amine by stirring the amine with one equivalent of carboxyl diimidazole in a suitable solvent such as dichloromethane at room temperature, and then evaporating to dryness *in vacuo*.

More specifically hexahydro-pyridoisoquinoline starting materials may prepared by methods analogous to those described in J. Pharm Bull, 1960, 8, 14.

Hexahydropyrroloisoquinolinylamines may prepared by methods analogous to those described in WO 97/17344.

Compounds of formula (III) are commercially available or may be prepared by conventional manipulation of substituents on commercially available substituted heterocyclic compounds. Alternatively, compounds of formula (III) may be synthesised by conventional procedures for preparation of tetrahydroisoquinoline, tetrahydroquinoline or dihydroindole compounds with desired substituents *in situ*. Gem-dialkylated indolines can be prepared according to literature methods e.g. T.W. Ramsay, G. R. Slater and P. Smith, Synthetic Comm. 1995, **25**, 4029. Compounds of formula (III) wherein Q is hydrogen or C1-6alkyl are commercially available or can be made from conventional nitration/reduction procedures. Alternatively, these compounds may be made from commercially available carboxylic acids via the Curtius rearrangement (Thornton T J. Synthesis 295 (1990).

Where the above described intermediates are novel compounds, they also form part of this invention.

The preparation of intermediates and starting materials for the process of this invention is illustrated by the following **Descriptions**; the preparation of compounds of this invention is illustrated by the following **Examples**. The utility of compounds of this invention is shown by the **Pharmacological Data** that follow the Examples.

Description 1

(+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline and (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline

From the nitration of 1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (3.5g) according to the method of WO 97/17344 (+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (0.35g) and (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (3.6g) were isolated by column chromatography (silica gel, 10% methanol:diethyl ether).

Description D1a: Characterisation of (+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline

^{1}H NMR (400MHz, $CDCl_3$) δ:1.70 - 1.81 (1H, m), 1.86 - 2.05 (2H, m), 2.37 - 2.43 (1H, m), 2.52 - 2.64 (2H, m), 3.07 - 3.47 (5H, m), 7.24 - 7.35 (2H, m) and 7.77 (1H, d, 7.16Hz).

Description D1b: Characterisation of (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline

^{1}H NMR (250MHz, $CDCl_3$) δ:1.72 – 2.01 (3H, m), 2.47 – 2.70 (3H, m), 2.90 – 3.10 (1H, m), 3.10 – 3.32 (3H, m), 3.39 (1H, t), 7.27 (1H, d, J = 8.3Hz), 7.95 (1H, s) and 7.99 (1H, dd, J = 2.3, 8.3Hz)

MS $^m/_z$ (API): 219 (MH^+; 100%).

Description 2

(+/-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-7-ylamine

A solution of nitro compound D1a (0.30g) in ethanol (20ml) and palladium on charcoal (5% w/w, 0.1g) was hydrogenated at 50psi at room temperature for 2h. The reaction mixture was filtered through a celite pad and the filtrate evaporated to dryness to give the title compound (0.22g) as an oil.

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.67 - 2.00 (3H, m), 2.27 - 2.82 (5H, m), 3.12 (1H, dt, J = 2.62 and 7.99Hz), 3.25 - 3.34 (2H, m), 6.54 (2H, d, J = 7.75Hz) and 6.98 (1H, t, J = 7.69).

MS $^m/_z$ (API): 189 (MH^+; 100%)

Description 3

(+/-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine

From nitro compound D1b (4.0g) the title compound (3.5g) was prepared according to the method of Description 2.

^{1}H NMR (250MHz, $CDCl_3$) 1.63 – 2.03 (3H, m), 2.23 – 2.38 (1H, m), 2.49 – 2.78 (3H, m), 2.93 – 3.24 (3H, m), 3.39 (1H, t), 6.42 (1H, d, J = 2.3Hz), 6.50 (1H, dd, J = 2.4, 7.9Hz) and 6.90 (1H, d, J = 7.9Hz).

MS $^m/_z$ (API): 189 (MH^+; 100%).

Description 4

(+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline and (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline.

(+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D1b) (50g) was separated into the two enantiomers by simulated moving bed chromatography using eight columns packed with 30g of Chiralpak AD and 10% ethanol in hexane (containing 0.1% diethylamine) as the eluant with the following system parameters: recycle flow rate = 101.64ml/min, feed = 1.04ml/min, eluent = 20.21ml/min, raffinate = 5.78ml/min, extract = 15.48ml/min, feed concentration = 9g/l, switch period = 1.18min. 19g of each enantiomer (e.e. >95%) was obtained.

First eluting component (+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4a)

Second eluting component (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4b)

Description 5

(-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine

From (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4b) (0.5g) the title compound (0.454g) was prepared according to the method of Description 2 using 5%pd/C (0.2g) and hydrogenating for 45min at room temperature..

Spectral data identical to the compound of Description 3.

$[\alpha]_D^{25}$ -111° (c 1.0, MeOH).

Description 6

(+)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine

From (+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4a) (0.25g) the title compound (0.183g) was prepared according to the method of Description 2 using 5%pd/C (0.15g) and hydrogenating for 45min at room temperature..

Spectral data identical to the compound of Description 3.

$[\alpha]_D^{25}$ +123° (c 0.5, MeOH).

Example 1

(+/-) 3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide and (+/-) 3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide hydrochloride

A solution of amine D3 (0.188g) in dichloromethane was treated with carbonyl diimidazole (0.245g) and stirred for 45min. Solvent was removed at reduced pressure, the residue dissolved in dimethylformamide (10ml) and 3,3-dimethylindoline (0.22g) added. The mixture was stirred overnight, diluted with

ethyl acetate and washed with water (65 x 25ml). The organic phase was dried (MgSO4), solvent removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane/methanol 19:1 eluant) to give the title compound (0.01g).

^{1}H NMR (250MHz, $CDCl_3$) δ: 1.39 (6H, s), 1.68 - 2.02 (3H, m), 2.31 - 2.45 (1H, m), 2.53 (1H, t), 2.65 (1H, dt), 2.76 - 2.86 (1H, m), 3.02 - 3.28 (3H, m), 3.45 (1H, t), 6.42 (1H, br. s), 6.99 - 7.26 (6H, m) and 7.87 (1H, d).

MS $^m/_z$ (API): 362 (MH^+; 100%)

The hydrochloride salt was prepared from the free base (0.13g) in methanol (5ml) by addition of ethereal HCl (1M, 2ml). Solvent was removed at reduced presure and the residue triturated to give the salt (0.11g)

^{1}H NMR (250MHz, $CDCl_3$) all resonances broadened δ: 1.37(6H, s), 2.04(3H, br. s), 2.62 (1H br. s), 2.82 (1H, br. d), 2.94 - 3.31 (3H, m) 3.45(1H, br. s.), 3.82 (1H, br. s.), 3.99(2H, s), 4.57 (1H, br. s.) 5.29 (1H, s), 6.87 - 7.24 (3H, m), 7.49 (2H, m), 7.67 (1H, br. s.), 7.93 (1H, d) and 12.54 (1H, br. s.).

Example 2

(+/-) 1-(3-Nitrophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

A solution of amine D3 (0.19g) in toluene (10ml) was treated with 3-nitrophenylisocyanate (0.164g) and mixture shaken at room temperature overnight. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane:methanol, 9:1) to give the title compound (0.35g) after conversion to the hydrochloride.

MS $^m/_z$ (API): 352 (MH^+; 100%)

Example 3

(+/-) 1-(3-Methoxyphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.24g) was prepared from amine D3 (0.19g) and 3-methoxyphenyl isocyanate (0.15g) according to the method of example 2.

MS $^m/_z$ (API): 337 (MH^+; 100%)

Example 4

(+/-) 1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.14g) was prepared from amine D3 (0.19g) and 3-ethylphenyl isocyanate (0.147g) according to the method of example 2.

MS $^m/_z$ (API): 336 (MH^+; 100%)

Example 5

(+/-) 1-(3-Methylthiophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.27g) was prepared from amine D3 (0.19g) and 3-methylthiophenyl isocyanate (0.165g) according to the method of example 2.

MS $^{m}/_{z}$ (API): 354 (MH^+; 100%)

Example 6

(+/-) 1-(3-Fluorophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.18g) was prepared from amine D3 (0.19g) and 3-fluorophenyl isocyanate (0.137g) according to the method of example 2.

MS $^{m}/_{z}$ (API): 354 (MH^+; 100%)

Example 7

(+/-) 1-(3-Trifluoromethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)thiourea hydrochloride

The title compound (0.18g) was prepared from amine D3 (0.19g) and 3-trifluoromethylphenyl isothiocyanate (0.203g) according to the method of example 2.

MS $^{m}/_{z}$ (API): 392 (MH^+; 100%)

Example 8

(+) 3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide hydrochloride

The title compound (0.19g) was prepared from amine D6 (0.19g) and 3,3-dimethylindoline (0.11g) according to the method of example 1.

MS $^{m}/_{z}$ (API): 362 (MH^+; 100%)

Example 9

(+) 1-(3-Bromophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.042g) was prepared from amine D6 (0.14g) and 3-bromophenyl aniline (0.13g) according to the method of example 1.

MS $^{m}/_{z}$ (API): 386, 388 (MH^+; 100%)

Example 10

(+) 1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea hydrochloride

The title compound (0.09g) was prepared from amine D6 (0.14g) and 3-bromophenyl aniline (0.13g) according to the method of example 1.
^{1}H NMR (250MHz, $CDCl_3$) δ 1.13 (3H, t, J = 7.5Hz), 1.55 – 1.67 (1H, m), 1.73 – 1.89 (2H, m), 2.17 (1H, m), 2.41 – 2.57 (4H, m), 2.65 – 2.73 (1H, m), 2.90 – 3.13 (3H, m), 3.24 (1H, m), 6.84 (1H, d, J = 7.2Hz), 6.92 (2H, s), 7.03 – 7.19 (4H, m) and 7.66 (2H, br. d).
MS $^m/_z$ (API): 336(MH^+; 100%)

PHARMACOGICAL DATA

1. Binding Assay Method

WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound A). It has been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 μM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of this invention were active in this test with pKi values greater than 6. For example, the compound of Example 1 gave a pKi value greater than 8.5

2. MEST Test

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties[1]. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method for mouse model

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and standard error required to induce a tonic seizure in 50% (CC_{50}) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CC_{50} is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

Studies are carried out using a Hugo Sachs Electronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

Method for rat model

The threshold for maximal (tonic hindlimb extension) electroshock seizures in male rats (Sprague Dawley, 80 - 150g, 6 weeks old) was determined by

a Hugo Sachs Electronik stimulator which delivered a constant current (0.3 sec duration; from 1-300mA in steps of 5-20mA). . The procedure is similar to that outlined above for mouse and full details are as published by Upton et al,.[4]

The percentage increase or decrease in CC_{50} for each group compared to the control is calculated.

Drugs are suspended in 1% methyl cellulose.

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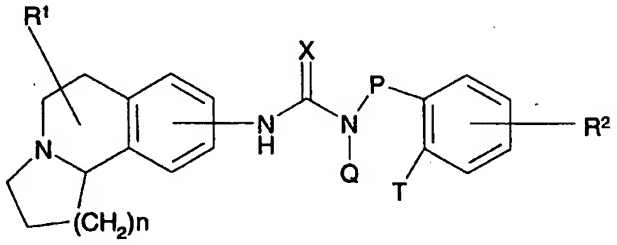
Results for rat MEST

Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing show an increase in seizure threshold. For example, the product of Example 1 showed a statistically significant increase (410 %) when examined in the rat model at a dose of 2 mg/kg p.o.

Claims

1. A compound of formula (I) or salt thereof or solvate thereof:



(I)

in which
P is a single bond, methylene or ethylene;
Q is hydrogen or C1-6alkyl;
T is hydrogen;
or Q and T together are $-(CH_2)_m-$ wherein the saturated ring formed thereby may be substituted by a group R^3;
m is 1 or 2;
n is 1 or 2;
X is O or S;
R^1, which may be at any position within the bicyclic saturated ring system, is hydrogen or up to two substituents which may be the same or different and each of which is selected from fluoro and C_{1-6} alkyl;
R^2 is hydrogen or up to four substituents independently selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, oxazolyl, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO_2-, $(C_{1-4}alkyl)_2NSO_2-$, $(C_{1-4}alkyl)NHSO_2-$, $(C_{1-4}alkyl)_2NCO-$, $(C_{1-4}alkyl)NHCO-$ or $CONH_2$;
or $-NR^4R^5$ where R^4 is hydrogen or C_{1-4} alkyl, and R^5 is hydrogen, C_{1-4}alkyl, formyl, $-CO_2C_{1-4}$alkyl or $-COC_{1-4}$alkyl;
R^3 is hydrogen or up to two C_{1-6} alkyl groups.

2. A compound of formula (I) according to claim1 having
R^1 as hydrogen, fluoro, methyl, ethyl or propyl,
R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl,

t-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl,
R^3 as hydrogen or methyl or gem-dimethyl.

3. A compound of formula (I) according to claim 1 or claim 2 wherein
R^1 is hydrogen,
R^2 is hydrogen or one or more of ethyl, methoxy, trifluoromethyl, cyano, chloro, fluoro,
R^3 is hydrogen or gem-dimethyl.

4. A compound of formula (I) according to any one of the preceding claims selected from:
3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide;
1-(3-Nitrophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;
1-(3-Methoxyphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;
1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;
1-(3-Methylthiophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;
1-(3-Fluorophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea;
1-(3-Trifluoromethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)thiourea;
3,3-Dimethyl-2,3-dihydroindole-1-carboxylic acid (1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)amide;
1-(3-Bromophenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea, and;
1-(3-Ethylphenyl)-3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)urea.

5. A pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other

degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

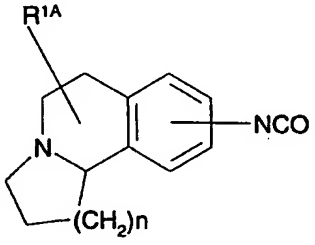
6. A method of treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof.

7. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases

such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

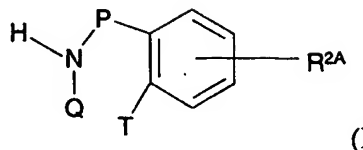
8. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

9. A process for the preparation of compounds of formula (I) as defined in claim 1 or salt thereof or solvate thereof, which comprises reacting a compound of formula (II)



(II)

where n is as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1,
with a compound of formula (III)



(III)

where P, Q, and T are as defined for formula (I), and when Q and T together are $-(CH_2)_m-$, the saturated ring formed thereby may be unsubstituted or substituted by a group R^{3A};
R^{2A} and R^{3A} are R^2 and R^3 respectively as defined for formula (I) or a group or groups convertible to R^2 or R^3;
and where required converting a R^{1A}, R^{2A} or R^{3A} group to a R^1, R^2 or R^3 group;
converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group;
converting a salt product to the free base or another salt which is pharmaceutically acceptable, or converting a free base product to a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05585

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 C07D455/06 A61K31/4375
//(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 39382 A (FUJISAWA PHARMACEUTICAL CO) 12 December 1996 (1996-12-12) page 17, line 22 - line 33; claim 1	1,5
P,A	WO 99 14197 A (SMITHKLINE BEECHAM PLC) 25 March 1999 (1999-03-25) claims 1,7	1,5
P,A	WO 99 25709 A (SMITHKLINE BEECHAN PLC) 27 May 1999 (1999-05-27) claims 1,7	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 1999	11/01/2000

Name and mailing address of the ISA
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/ 05585

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5 to 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 5 to 8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]national Application No
PCT/EP 99/05585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639382 A	12-12-1996	JP 11506468 T	08-06-1999
WO 9914197 A	25-03-1999	NONE	
WO 9925709 A	27-05-1999	NONE	